Non-cardiac comorbidities in heart failure with preserved ejection fraction

Streng, Koen Wouter

Chapter 1

Introduction

INTRODUCTION

Heart failure is a clinical syndrome with symptoms of dyspnoea, fatigue and impaired exercise tolerance caused by structural or functional abnormality of the heart. The prevalence of heart failure is still rising, and is currently prevalent in around 1-2 per cent in Western countries. The estimated incidence of heart failure in the elderly population in the Netherlands raises up to 12.4 per 1000 persons aged above 85 years. Due to its rising prevalence and its high mortality and hospitalization rates, heart failure is a major burden for the patients but also for our health care costs.[1,2]

Heart failure can be categorized into three groups based on left ventricular ejection fraction (LVEF). Heart failure with reduced ejection fraction (HFrEF) is considered to be the classical form of heart failure. In the beginning of this millennium, it became clear that there are patients who presented with identical signs and symptoms of heart failure, but had a normal LVEF. These patients were classified as patients with heart failure with preserved ejection fraction (HFpEF). However, there was a grey area present within this classification, since patients with a moderately reduced ejection fraction were neither HFrEF patients nor HFpEF patients. In 2016 the European Society of Cardiology presented new heart failure guidelines, and provided distinct cut-offs for LVEF; HFrEF was defined as an LVEF below 40%, HFpEF as equal or above 50%, and patients in the former grey area were classified as heart failure with mid-range ejection fraction (HFmrEF) with an LVEF between 40 and 49%.[3] Categorizing these groups is essential since patient characteristics in these groups are very different, and where there are treatment options available for reducing mortality and hospitalization in patients with reduced ejection fraction, these therapies are not available for patients with heart failure with preserved ejection fraction. Instead, patients with HFpEF are mainly treated for their symptoms by prescribing diuretics.

HFpEF currently accounts for over half of all heart failure cases, and the population burden is only expected to rise in the upcoming decades.[4] These patients are predominantly elderly women and are often accompanied by a number of concurrent diseases, referred to as comorbidities. Recent data suggest that around 75% of the heart failure patients has at least one comorbidity, of which renal disease, anaemia and diabetes mellitus are most common.[5,6] These comorbidities often interfere with the current treatment for heart failure patients. For example renal dysfunction limits the use of ACE-inhibitors.

A major contributing factor for the high prevalence of comorbidities could be the higher age in patients with HFpEF. However, comorbidities themselves could also contribute

to the onset and progression of HFpEF, resulting in a more systemic disease. A number of studies have shown that the phenotype of HFpEF is complex, and at least partially defined by accompanying comorbidities.[7-9] Some have even suggested that HFpEF is not more than a collection of comorbidities.[10] Within the comorbidities, we differentiate between cardiac comorbidities and non-cardiac comorbidities. This thesis will focus on two important non-cardiac comorbidities: Obesity and renal dysfunction.

The first aim of this thesis is to assess the prevalence of non-cardiac comorbidities in patients with HFrEF, HFmrEF and HFpEF and the associations between these comorbidities and clinical outcome

Non-cardiac comorbidities are often associated with higher mortality and hospitalization rates, and are highly prevalent in patients with heart failure.[11,12] However, the association between each of the individual comorbidities in patients with heart failure is unknown, as well as their association with quality of life in these patients. Quality of life is often underestimated, with treatment options focussing on reducing mortality and hospitalization and not on softer endpoints. However, quality of life is of great importance to patients, and identifying comorbidities which influence quality of life could therefore be meaningful.

In **Chapter 2**, we study the prevalence of eight different non-cardiac comorbidities in patients with HFrEF, HFmrEF and HFpEF in two combined large heart failure cohorts. Furthermore we assess their individual association with quality of life, mortality and hospitalization.

One of the highly prevalent non-cardiac comorbidities in patients with HFpEF is obesity, often defined as a body mass index equal or above 30 kg/m^2. Obesity is an ongoing burden to society with a growing prevalence, especially in developed countries. Over one-third of the adults in the United Stated has obesity, and this trend shows an epidemic spread around the rest of the world.[13] Obesity is a risk factor for the onset of heart failure, partly due to its relation with hypertension, diabetes mellitus and coronary artery disease.[14,15] However, obesity could also interfere with the diagnosis of heart failure. Physical examination could be impeded, where pulmonary auscultation is difficult, and echocardiographic images are often of poor quality. Furthermore, brain natriuretic peptides (BNP) are important for the diagnosis of heart failure, but obesity is also known to negatively influence levels of BNP.[16] However, if this holds true for other biomarkers, and if body mass index influences the prognostic value of these markers, is unknown. Therefore, **Chapter 3** focusses on the association of body mass index with

different laboratory and biomarkers in acute heart failure, and we investigate whether this influences the predictive value of these biomarkers on mortality.

Nevertheless, obesity in heart failure is not only negatively portrayed in the literature. In patients with established heart failure there is a so-called obesity paradox. This paradox refers to the phenomenon that a higher body mass index is related to worse cardiovascular outcomes in non-heart failure patients, while in patients with heart failure a higher body mass index is related to better cardiovascular outcomes. The best survival rates are seen in patients with a body mass index between 25 and 35 kg/m^2, and their outcome is better than underweight patients with heart failure or those with a normal body mass index (between 20-25 kg/m^2).[17-20] However, this paradox is mainly described using body mass index to define obesity, which only gives limited information about fat distribution in the body, and therefore poorly distinguishes between fitness and fatness in a patient.[21,22] The obesity paradox remains an incomplete understood phenomenon, which might be partially caused by the limitations of solely assessing body mass index in these patients. A more comprehensive assessment of the patient by additional measurements using other indices, such as waist and/or hip circumference, could provide more information about fat distribution in the patient.

Therefore the second aim of this thesis is to study the association of obesity and nutritional status in patients with heart failure and clinical outcome.

In **Chapter 4** we study the association of waist-to-hip ratio and mortality in heart failure patients, and show the additive value of different assessments besides body mass index in these patients. Besides fat distribution, nutrition could also play an important role in patients with heart failure. Proteins are an essential part of a healthy diet, and are present in a variety of foods. Proteins are used to form amino acids and building up muscle mass, and are known to be beneficial in the general population. However, if protein intake has any association with mortality in a heart failure population is unknown. Therefore **Chapter 5** sets out to assess the association of estimated protein intake through a urinary marker in a large heart failure cohort, and identifies whether protein intake is associated with mortality in patients with heart failure.

Another highly prevalent non-cardiac comorbidity in patients with heart failure is renal dysfunction, being prevalent in around half of the patients with heart failure.[6,23] Renal dysfunction and heart failure often co-exist, and is commonly referred to as the cardiorenal syndrome. Renal dysfunction may worsen heart failure, or vice versa heart failure may worsen renal dysfunction via low cardiac output and increased central venous pressure. Furthermore, shared risk factors like diabetes and hypertension may play a

role in the onset or progression of cardiac and renal dysfunction. Renal dysfunction in heart failure has been extensively studied over the past years. However, the majority of studies have been performed in patients with HFrEF. Much less is known about the mechanisms related to cardiac and renal failure in patients with HFpEF. In patients with HFpEF the pathophysiology behind renal dysfunction might be different from patients with HFrEF. For example, endothelial dysfunction and chronic low grade state of inflammation have been recently linked to renal dysfunction and HFpEF. However, these mechanisms have not been fully understood.[24] In the second part of this thesis we therefore aimed to provide more insight in renal dysfunction in patients with HFpEF and HFrEF.

The third aim of this thesis is to use established and novel renal markers to explore the pathophysiology behind renal dysfunction in patients with HFrEF and HFpEF.

Chapter 6 is a meta-analysis regarding the use of renin-angiotensin aldosterone system (RAAS) inhibitors in patients with HFrEF and patients with HFpEF, and assesses the association of a RAAS inhibitor induced worsening renal function and the association with mortality in these patients. In **Chapter 7**, we examine several urinary markers in a large chronic heart failure cohort, to study the pathophysiology behind the differences in renal dysfunction between patients with HFrEF and patients with HFpEF. Via several urinary markers we aimed to investigate the potential differences in nephron segment damage in patients with HFrEF and HFpEF.

Finally, **Chapter 8** discusses the main findings and the relevance of this thesis, and places these results into perspective and describes future directions and possibilities.

References

1. Braunschweig F, Cowie MR, Auricchio A. What are the costs of heart failure? Europace 2011;13 Suppl 2:ii13-7.
2. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, Allison M, Hemingway H, Cleland JG, McMurray JJV, Rahimi K. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet 2018;391:572-580.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-2200.
4. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 2017;
5. Mentz RJ, Kelly JP, von Lueder TG, Voors AA, Lam CS, Cowie MR, Kjeldsen K, Jankowska EA, Atar D, Butler J, Fiuzat M, Zannad F, Pitt B, O'Connor CM. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. J Am Coll Cardiol 2014;64:2281-2293.
6. van Deursen VM, Urso R, Laroche C, Damman K, Dahlstrom U, Tavazzi L, Maggioni AP, Voors AA. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. Eur J Heart Fail 2014;16:103-111.
7. Mentz RJ, Kelly JP, von Lueder TG, Voors AA, Lam CS, Cowie MR, Kjeldsen K, Jankowska EA, Atar D, Butler J, Fiuzat M, Zannad F, Pitt B, O'Connor CM. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. J Am Coll Cardiol 2014;64:2281-2293.
8. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013;62:263-271.
9. Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, Paulus WJ. Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction: A Multiorgan Roadmap. Circulation 2016;134:73-90.
10. Packer M. Can brain natriuretic peptide be used to guide the management of patients with heart failure and a preserved ejection fraction? The wrong way to identify new treatments for a nonexistent disease. Circ Heart Fail 2011;4:538-540.
11. van Deursen VM, Damman K, van der Meer P, Wijkstra PJ, Luijckx GJ, van Beek A, van Veldhuisen DJ, Voors AA. Co-morbidities in heart failure. Heart Fail Rev 2014;19:163-172.
12. Baldi I, Azzolina D, Berchialla P, Gregori D, Scotti L, Corrao G. Comorbidity-adjusted relative survival in newly hospitalized heart failure patients: A population-based study. Int J Cardiol 2017;243:385-388.

13. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA 2014;311:806-814.

14. Kenchaiah S, Sesso HD, Gaziano JM. Body mass index and vigorous physical activity and the risk of heart failure among men. Circulation 2009;119:44-52.

15. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. N Engl J Med 2002;347:305-313.

16. Madamanchi C, Alhosaini H, Sumida A, Runge MS. Obesity and natriuretic peptides, BNP and NT-proBNP: mechanisms and diagnostic implications for heart failure. Int J Cardiol 2014;176:611-617.

17. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. JACC Heart Fail 2013;1:93-102.

18. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. J Am Coll Cardiol 2001;38:789-795.

19. Lavie CJ, Sharma A, Alpert MA, De Schutter A, Lopez-Jimenez F, Milani RV, Ventura HO. Update on Obesity and Obesity Paradox in Heart Failure. Prog Cardiovasc Dis 2016;58:393-400.

20. Shah R, Gayat E, Januzzi JL,Jr, Sato N, Cohen-Solal A, diSomma S, Fairman E, Harjola VP, Ishihara S, Lassus J, Maggioni A, Metra M, Mueller C, Mueller T, Parenica J, Pascual-Figal D, Peacock WF, Spinar J, van Kimmenade R, Mebazaa A, GREAT (Global Research on Acute Conditions Team) Network. Body mass index and mortality in acutely decompensated heart failure across the world: a global obesity paradox. J Am Coll Cardiol 2014;63:778-785.

21. Piepoli MF, Corra U, Veglia F, Bonomi A, Salvioni E, Cattadori G, Metra M, Lombardi C, Sinagra G, Limongelli G, Raimondo R, Re F, Magri D, Belardinelli R, Parati G, Mina C, Scardovi AB, Guazzi M, Cicoira M, Scrutinio D, Di Lenarda A, Bussotti M, Frigerio M, Correale M, Villani GQ, Paolillo S, Passino C, Agostoni P, MECKI Score Research Group. Exercise tolerance can explain the obesity paradox in patients with systolic heart failure: data from the MECKI Score Research Group. Eur J Heart Fail 2016;18:545-553.

22. Lavie CJ, De Schutter A, Milani RV. Healthy obese versus unhealthy lean: the obesity paradox. Nat Rev Endocrinol 2015;11:55-62.

23. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J 2014;35:455-469.

24. Ter Maaten JM, Damman K, Verhaar MC, Paulus WJ, Duncker DJ, Cheng C, van Heerebeek L, Hillege HL, Lam CS, Navis G, Voors AA. Connecting heart failure with preserved ejection fraction and renal dysfunction: the role of endothelial dysfunction and inflammation. Eur J Heart Fail 2016;18:588-598.